

REMARKS

Formal Matters

The present application has been amended to insert the Sequence Listing and corresponding SEQ ID NOS.

No new matter is added.

In the above amendment, originally filed Figures 2A, 2B, 2C and Figure 3 have been replaced with the enclosed new Figures 2A, 2B, 2C and Figure 3. In the newly submitted Figures 2A, 2B, 2C and Figure 3, the requisite SEQ ID NOS have been provided. Originally filed Figures 2A, 2B, 2C and Figure 3 with the amendments shown in red are also enclosed.

It is respectfully requested that the Examiner enter the newly submitted Figures 2A, 2B, 2C and Figure 3.

Certification Regarding Sequence Listing

I hereby certify that the enclosed Sequence Listing is being submitted under 37 CFR §§ 1.821(c) and (e) in paper and computer readable form (Compact Disk labeled 'CRF').

As required by 37 CFR 1.821(f), I hereby state that the content of the paper and computer readable copy of the Sequence Listing, submitted in accordance with 37 C.F.R. §1.821(c) and (e) are the same. The Computer Readable Format (CRF), being submitted under 37 CFR §§ 1.52(e) and 1.824, is formatted on IBM-PC, the operating system compatibility is MS-Windows and the file listing is:

Seqlist.txt 10.8 KB created December 4, 2002.

I hereby certify that the enclosed submission includes no new matter. The Sequence Listing was prepared with the software FASTSEQ, and conforms to the Patent Office guidelines. Applicant respectfully submits that the subject application is in adherence to 37 CFR §§ 1.821-1.825.

Respectfully submitted,

Dated: 12.5.02

By: 

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Registration No. 37,620

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“Version with Markings to Show Changes Made”

In the Specification:

In the section entitled “BRIEF DESCRIPTION OF THE DRAWINGS”, please replace paragraphs 10 and 11 with the corresponding paragraphs below:

[0010] Figure 2 is the DNA (SEQ ID NO: 13) and amino acid sequence (SEQ ID NO: 14) of the vector presented in Figure 1. The start of translation is denoted by lower case type in the amino acid sequence, the affinity purification peptide is denoted with lower case bold type in the amino acid sequence, and the enterokinase cDNA is denoted with lowercase bold type in both the DNA and amino acid sequences.

[0011] Figure 3 shows various DNA (SEQ ID NOS: 16-20) and amino acid sequence (SEQ ID NOS: 1-4, 15) embodiments of the affinity purification site of the present invention.

On page 13, please replace paragraph [0061] with the following paragraph:

In some embodiments, each of X_1 and X_2 is independently selected from the group consisting of Leu, Ile, Val, Ala, Gly, Asn, and Gln. In other embodiments, each of X_1 and X_2 is independently selected from the group consisting of Leu, Val, Asn, and Ile. In some embodiments, each of X_3 , X_4 , X_5 is independently selected from the group consisting of Lys, Arg, Asp, and Glu. In some embodiments, each of X_3 , X_4 , X_5 is independently selected from the group consisting of Lys and Glu. In some embodiments, each X_6 is independently selected from the group consisting of Leu, Ile, Val, Ala, Gly, Asn, and Gln. In other embodiments, each X_6 is independently selected from the group consisting of Ala and Asn. In one particular embodiment, the affinity peptide has the amino acid sequence $\text{NH}_2\text{-His-Leu-Ile-His-Asn-Val-His-Lys-Glu-Glu-His-Ala-His-Ala-His-Asn-COOH}$ (SEQ ID NO: 1).

A

On page 13, please replace paragraph [0063] with the following paragraph:

The invention further provides a metal ion affinity peptide, wherein the affinity peptide has the formula $(\text{His-}X_1\text{-}X_2)_n$, wherein each of X_1 and X_2 is an amino acid having an acidic side

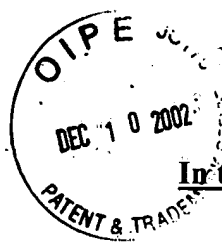
chain, and n=3 to 10. In one embodiment, the affinity peptide comprises the sequence (His-Asp-Asp)₆ (SEQ ID NO: 2). In another embodiment, the affinity peptide comprises the sequence (His-Glu-Glu)₆ (SEQ ID NO: 3). In a further embodiment, the affinity peptide comprises the sequence (His-Asp-Glu)₆ (SEQ ID NO: 4). In a further embodiment, the affinity peptide comprises the sequence (His-Glu-Asp)₆ (SEQ ID NO: 5).

On page 14, please replace paragraph [0068] with the following paragraph:

Proteolytic cleavage sites are known to those skilled in the art; a wide variety are known and have been described amply in the literature, including, e.g., Handbook of Proteolytic Enzymes (1998) AJ Barrett, ND Rawlings, and JF Woessner, eds., Academic Press. Proteolytic cleavage sites include, but are not limited to, an enterokinase cleavage site: (Asp)₄Lys (SEQ ID NO: 6); a factor Xa cleavage site: Ile-Glu-Gly-Arg (SEQ ID NO: 7); a thrombin cleavage site, e.g., Leu-Val-Pro-Arg-Gly-Ser (SEQ ID NO: 8); a renin cleavage site, e.g., His-Pro-Phe-His-Leu-Val-Ile-His (SEQ ID NO: 9); a collagenase cleavage site, e.g., X-Gly-Pro (where X is any amino acid); a trypsin cleavage site, e.g., Arg-Lys; a viral protease cleavage site, such as a viral 2A or 3C protease cleavage site, including, but not limited to, a protease 2A cleavage site from a picornavirus (see, e.g., Sommergruber et al. (1994) *Virol.* 198:741-745), a Hepatitis A virus 3C cleavage site (see, e.g., Schultheiss et al. (1995) *J. Virol.* 69:1727-1733), human rhinovirus 2A protease cleavage site (see, e.g., Wang et al. (1997) *Biochem. Biophys. Res. Comm.* 235:562-566), and a picornavirus 3 protease cleavage site (see, e.g., Walker et al. (1994) *Biotechnol.* 12:601-605).

On page 15, please replace paragraph [0063] with the following paragraph:

A subject fusion protein may comprise, in addition to a fusion partner polypeptide and a metal ion affinity peptide, an immunological tag. An immunological tag, if present, is present at the amino terminus, the carboxyl terminus, or disposed between the fusion partner polypeptide and the metal ion affinity peptide. Immunological tags are known in the art, and are typically a sequence of between about 6 and about 50 amino acids that comprise an epitope that is recognized by an antibody specific for the epitope. Non-limiting examples of such tags are hemagglutinin (HA; e.g., CYPYDVPDYA (SEQ ID NO: 10)), FLAG (e.g., DYKDDDDK (SEQ ID NO: 11)), c-myc (e.g., CEQKLISEEDL (SEQ ID NO: 12)), and the like.



In the Claims:

On page 36, please replace claims 8, 10-13 with the corresponding claims below:

8. The metal ion affinity peptide according to claim 1, wherein the metal ion affinity peptide is of formula 1, and wherein the affinity peptide has the amino acid sequence $\text{NH}_2\text{-His-Leu-Ile-His-Asn-Val-His-Lys-Glu-Glu-His-Ala-His-Ala-His-Asn-COOH}$ (SEQ ID NO: 1).

10. The metal ion affinity peptide according to claim 1, wherein the metal ion affinity peptide is of formula 3, and wherein the affinity peptide comprises the sequence (His-Asp-Asp)₆ (SEQ ID NO: 2).

11. The metal ion affinity peptide according to claim 1, wherein the metal ion affinity peptide is of formula 3, and wherein the affinity peptide comprises the sequence (His-Glu-Glu)₆ (SEQ ID NO: 3).

12. The metal ion affinity peptide according to claim 1, wherein the metal ion affinity peptide is of formula 3, and wherein the affinity peptide comprises the sequence (His-Asp-Glu)₆ (SEQ ID NO: 4).

13. The metal ion affinity peptide according to claim 1, wherein the metal ion affinity peptide is of formula 3, and wherein the affinity peptide comprises the sequence (His-Glu-Asp)₆ (SEQ ID NO: 5).

In the drawings:

Please replace Figures 2A, 2B, 2C and Figure 3 with clean copies of the corresponding Figures, attached herewith.



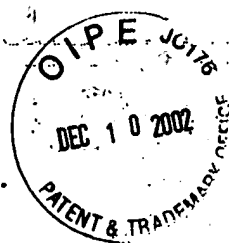
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61/21	91/31
CTT AGA CGT CAG GTG GCA CTT TTC GGG GAA	ATG TGC GCG GAA CCC CTA TTT GTT TAT TTT
121/41	151/51
TCT AAA TAC ATT CAA ATA TGT ATC CGC TCA	TGA GAC AAT AAC CCT GAT AAA TGC TTC AAT
181/61	211/71
AAT ATT GAA AAA GGA AGA GTA TGA GTA TTC	AAC ATT TCC GTG TCG CCC TTA TTC CCT TTT
241/81	271/91
TTG CGG CAT TTT GCC TTC CTG TTT TTG CTC	ACC CAG AAA CGC TGG TGA AAG TAA AAG ATG
301/101	331/111
CTG AAG ATC AGT TGG GTG CAC GAG TGG GTT	ACA TCG AAC TGG ATC TCA ACA GCG GTA AGA
361/121	391/131
TCC TTG AGA GTT TTC GCC CCG AAG AAC GTT	TTC CAA TGA TGA GCA CTT TTA AAG TTC TGC
421/141	451/151
TAT GTG GCG CGG TAT TAT CCC GTA TTG ACG	CCG GGC AAG AGC AAC TCG GTC GCC GCA TAC
481/161	511/171
ACT ATT CTC AGA ATG ACT TGG TTG AGT ACT	CAC CAG TCA CAG AAA AGC ATC TTA CGG ATG
541/181	571/191
GCA TGA CAG TAA GAG AAT TAT GCA GTG CTG	CCA TAA CCA TGA GTG ATA ACA CTG CGG CCA
601/201	631/211
ACT TAC TTC TGA CAA CGA TCG GAG GAC CGA	AGG AGC TAA CCG CTT TTT TGC ACA ACA TGG
661/221	691/231
GGG ATC ATG TAA CTC GCC TTG ATC GTT GGG	AAC CGG AGC TGA ATG AAG CCA TAC CAA ACG
721/241	751/251
ACG AGC GTG ACA CCA CGA TGC CTG TAG CAA	TGG CAA CAA CGT TGC GCA AAC TAT TAA CTG
781/261	811/271
GCG AAC TAC TTA CTC TAG CTT CCC GGC AAC	AAT TAA TAG ACT GGA TGG AGG CGG ATA AAG
841/281	871/291
TTG CAG GAC CAC TTC TGC GCT CGG CCC TTC	CGG CTG GCT GGT TTA TTG CTG ATA AAT CTG
901/301	931/311
GAG CCG GTG AGC GTG GGT CTC GCG GTA TCA	TTG CAG CAC TGG GGC CAG ATG GTA AGC CCT
961/321	991/331
CCC GTA TCG TAG TTA TCT ACA CGA CGG GGA	GTC AGG CAA CTA TGG ATG AAC GAA ATA GAC
1021/341	1051/351
AGA TCG CTG AGA TAG GTG CCT CAC TGA TTA	AGC ATT GGT AAC TGT CAG ACC AAG TTT ACT
1081/361	1111/371
CAT ATA TAC TTT AGA TTG ATT TAA AAC TTC	ATT TTT AAT TTA AAA GGA TCT AGG TGA AGA
1141/381	1171/391
TCC TTT TTG ATA ATC TCA TGA CCA AAA TCC	CTT AAC GTG AGT TTT CGT TCC ACT GAG CTT
1201/401	1231/411
CAG ACC CCG TAG AAA AGA TCA AAG GAT CTT	CTT GAG ATC CTT TTT TTC TGC GCG TAA TCT
1261/421	1291/431
GCT GCT TGC AAA CAA AAA AAC CAC CGC TAC	CAG CGG TGG TTT GTT TGC CGG ATC AAG AGC
1321/441	1351/451
TAC CAA CTC TTT TTC CGA AGG TAA CTG GCT	TCA GCA GAG CGC AGA TAC CAA ATA CTG TCC
1381/461	1411/471
TTC TAG TGT AGC CGT AGT TAG GCC ACC ACT	TCA AGA ACT CTG TAG CAC CGC CTA CAT ACC
1441/481	1471/491
TCG CTC TGC TAA TCC TGT TAC CAG TGG CTG	CTG CCA GTG GCG ATA AGT CGT GTC TTA CCG
1501/501	1531/511
GGT TGG ACT CAA GAC GAT AGT TAC CGG ATA	AGG CCG AGC GGT CGG GCT GAA CGG GGG GTT
1561/521	1591/531
CGT GCA CAC AGC CCA GCT TGG AGC GAA CGA	CCT ACA CCG AAC TGA GAT ACC TAC AGC GTG
1621/541	1651/551
AGC TAT GAG AAA GCG CCA CGC TTC CCG AAG	GCA GAA AGG CGG ACA GGT ATC CGG TAA GCG

FIGURE 2A (SEQ ID NO: 13)

OTPE JG13
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1681/561	GCA GGG TCG GAA CAG GAG AGC GCA CGA GGG	1711/571	AGC TTC CAG GGG GAA ACG CCT GGT ATC TTT
1741/581	ATA GTC CTG TCG GGT TTC GCC ACC TCT GAC	1771/591	TTG AGC GTC GAT TTT TGT GAT GCT CGT CAG
1801/601	GGG GGC GGA GCC TAT GGA AAA ACG CCA GCA	1831/611	ACG CGG CCT TTT TAC GGT TCC TGG CCT TTT
1861/621	GCT GGC CTT TTG CTC ACA TGT TCT TTC CTG	1891/631	CGT TAT CCC CTG ATT CTG TGG ATA ACC GTA
1921/641	TTA CCG CCT TTG AGT GAG CTG ATA CCG CTC	1951/651	GCC GCA GCC GAA CGA CCG AGC GCA GCG AGT
1981/661	leu pro pro leu ser glu leu ile pro leu	2011/671	ala ala ala glu arg pro ser ala ala ser
2041/681	CAG TGA GCG AGG AAG CCG AAG AGC GCC CAA	2071/691	TAC GCA AAC CGC CTC TCC CCG CGC GTT GGC
2101/701	gln opa ala arg lys arg lys ser ala gln	2131/711	tyr ala asn arg leu ser pro arg val gly
2161/721	CGA TTC ATT AAT GCA GCT GGC ACG ACA GGT	2191/731	TTC CCG ACT GGA AAG CCG GCA GTG AGC GCA
2221/741	arg phe ile asn ala ala gly thr thr gly	2251/751	phe pro thr gly lys arg ala val ser ala
2281/761	ACC CAA TTA ATG TGA GTT AGC TCA CTC ATT	2311/771	AGG CAC CCC AGG CTT TAC ACT TTA TGC TTC
2341/781	CGG CTC GTA TGT TGT GTG GAA TTG TGA GCG	2371/791	GAT AAC AAT TTC ACA CAG GAA ACA GCT atg
2401/801			met
2461/821	acc atg att acg cca agc ttg AAG GAT CAT	2491/831	CTC ATC CAC AAT GTC CAC AAA GAG GAG CAC
2521/841	thr met ile thr pro ser leu lys asp his	2551/851	leu ile his asn val his lys glu glu his
2581/861	GCT CAT GCC CAC AAC AAG ATC GAT att gtc	2611/871	gga gga agt gac tcc aga gaa gga gcc tgg
2641/881	ala his ala his asn lys ile asp ile val	2671/891	gly gly ser asp ser arg glu gly ala trp
2701/901	cct tgg gtc gtt gct ctg tat ttc gac gat	2731/911	caa cag gtc tgc gga gct tct ctg gtg agc
2761/921	pro trp val val ala leu tyr phe asp asp	2791/931	gln gln val cys gly ala ser leu val ser
2821/941	agg gat tgg ctg gtg tgg gcc gcc cac tgc	2851/951	gtg tac ggg aga aat atg gag ccg tct aag
2881/961	arg asp trp leu val ser ala ala his cys	2911/971	val tyr gly arg asn met glu pro ser lys
2941/981	tgg aaa gca gtg cta ggc ctg cat atg gca	2971/991	tca aat ctg act tct cct cag ata gaa act
3001/1001	trp lys ala val leu gly leu his met ala		ser asn leu thr ser pro gln ile glu thr
	agg ttg att gac caa att gtc ata aac cca		cac tac aat aaa cgg aga aag aac aat gac
	arg leu ile asp gln ile val ile asn pro		his tyr asn lys arg arg lys asn asn asp
	att gcc atg atg cat ctt gaa atg aaa gtg		aac tac aca gat tat ata cag cct att tgt
	ile ala met met his leu glu met lys val		asn tyr thr asp tyr ile gln pro ile cys
	tta cca gaa gaa aat caa gtt ttt ccc cca		gga aga att tgt tct att gct ggc tgg ggg
	leu pro glu glu asn gln val phe pro pro		gly arg ile cys ser ile ala gly trp gly
	gca ctt ata tat caa ggt tct act gca gac		gta ctg caa gaa gct gac gtt ccc ctt cta
	ala leu ile tyr gln gly ser thr ala asp		val leu gln glu ala asp val pro leu leu
	tca aat gag aaa tgt caa caa cag atg cca		gaa tat aac att acg gaa aat atg gtg tgt
	ser asn glu lys cys gln gln gln met pro		glu tyr asn ile thr glu asn met val cys
	gca ggc tat gaa gca gga ggg gta gat tct		tgt cag ggg gat tca ggc gga cca ctc atg
	ala gly tyr glu ala gly gly val asp ser		cys gln gly asp ser gly gly pro leu met
	tgc caa gaa aac aac aga tgg ctc ctg gct		ggc gtg acg tca ttt gga tat caa tgt gca
	cys gln glu asn asn arg trp leu leu ala		gly val thr ser phe gly tyr gln cys ala
	ctg cct aat cgc cca ggg gtg tat gcc cgg		gtc cca agg ttc aca gag tgg ata caa agt
	leu pro asn arg pro gly val tyr ala arg		val pro arg phe thr glu trp ile gln ser
	ttt cta cat		GAG CTC GTA ATT AGC TGA GAA TTC ACT GGC CGT CGT TTT ACA ACG TCG TGA
	phe leu his		glu leu val ile ser opa glu phe thr gly arg arg phe thr thr ser opa

(SEQ ID NO: 13 (DNA SEQUENCE))
(SEQ ID NO: 14 (protein sequence))



3061/1021	3091/1031
CTG GGA AAA CCC TGG CGT TAC CCA ACT TAA	TCG CCT TGC AGC ACA TCC CCC TTT CGC CAG
3121/1041	3151/1051
CTG GCG TAA TAG CGA AGA GGC CCG CAC CGA	TCG CCC TTC CCA ACA GTT GCG CAG CCT GAA
3181/1061	3211/1071
TGG CGA ATG GCG CCT GAT GCG GTA TTT TCT	CCT TAC GCA TCT GTG CCG TAT TTC ACA CCG
3241/1081	3271/1091
CAT ATG GTG CAC TCT CAG TAC AAT CTG CTC	TGA TGC CGC ATA GTT AAG CCA GCC CCG ACA
3301/1101	3331/1111
CCC GCC AAC ACC CGC TGA CGC GCC CTG ACG	GGC TTG TCT GCT CCC GGC ATC CGC TTA CAG
3361/1121	3391/1131
ACA AGC TGT GAC CGT CTC CGG GAG CTG CAT	GTG TCA GAG GTT TTC ACC GTC ATC ACC GAA
3421/1141	
ACG CGC	

FIGURE 2C (SEQ ID NO: 13)



Insert 1

1/1 31/11
CAT CTC ATC CAC AAT GTC CAC AAA GAG GAG CAC GCT CAT GCC CAC AAC (SEQ ID NO: 16)
his leu ile his asn val his lys glu glu his ala his ala his asn (SEQ ID NO: 1)

Insert 2

1/1 31/11
CAT AAC CAT AAC CAT AAC CAT AAC CAT AAC CAT AAC (SEQ ID NO: 17)
his asn his asn his asn his asn his asn his asn his asn (SEQ ID NO: 15)

Insert 3

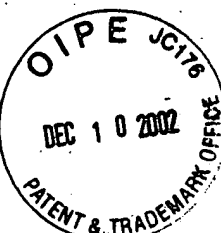
1/1 31/11
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his asp asp his asp asp his asp asp his asp asp his asp asp his asp asp (SEQ ID NO: 2)

Insert 4

1/1 31/11
CAT GAG GAG CAT GAG GAG CAT GAG GAG CAT GAG GAG CAT GAG GAG CAT GAG GAG (SEQ ID NO: 19)
his glu glu his glu glu his glu glu his glu glu his glu glu his glu glu (SEQ ID NO: 3)

Insert 5

1/1 31/11
CAT GAT GAG CAT GAT GAG CAT GAG AAC CAT GAG AAC CAT GAG GAT CAT GAG GAT (SEQ ID NO: 20)
his asp glu his asp glu his glu asn his glu asn his glu asp his glu asp (SEQ ID NO: 4)



1/1	31/11
GAC GAA AGG GCC TCG TGA TAC GCC TAT TTT	TAT AGG TTA ATG TCA TGA TAA TAA TGG TTT
61/21	91/31
CTT AGA CGT CAG GTG GCA CTT TTC GGG GAA	ATG TGC GCG GAA CCC CTA TTT GTT TAT TTT
121/41	151/51
TCT AAA TAC ATT CAA ATA TGT ATC CGC TCA	TGA GAC AAT AAC CCT GAT AAA TGC TTC AAT
181/61	211/71
AAT ATT GAA AAA GGA AGA GTA TGA GTA TTC	AAC ATT TCC GTG TCG CCC TTA TTC CCT TTT
241/81	271/91
TTG CGG CAT TTT GCC TTC CTG TTT TTG CTC	ACC CAG AAA CGC TGG TGA AAG TAA AAG ATG
301/101	331/111
CTG AAG ATC AGT TGG GTG CAC GAG TGG GTT	ACA TCG AAC TGG ATC TCA ACA GCG GTA AGA
361/121	391/131
TCC TTG AGA GTT TTC GCC CCG AAG AAC GTT	TTC CAA TGA TGA GCA CTT TTA AAG TTC TGC
421/141	451/151
TAT GTG GCG CGG TAT TAT CCC GTA TTG ACG	CCG GGC AAG AGC AAC TCG GTC GCC GCA TAC
481/161	511/171
ACT ATT CTC AGA ATG ACT TGG TTG AGT ACT	CAC CAG TCA CAG AAA AGC ATC TTA CGG ATG
541/181	571/191
GCA TGA CAG TAA GAG AAT TAT GCA GTG CTG	CCA TAA CCA TGA GTG ATA ACA CTG CGG CCA
601/201	631/211
ACT TAC TTC TGA CAA CGA TCG GAG GAC CGA	AGG AGC TAA CCG CTT TTT TGC ACA ACA TGG
661/221	691/231
GGG ATC ATG TAA CTC GCC TTG ATC GTT GGG	AAC CGG AGC TGA ATG AAG CCA TAC CAA ACG
721/241	751/251
ACG AGC GTG ACA CCA CGA TGC CTG TAG CAA	TGG CAA CAA CGT TGC GCA AAC TAT TAA CTG
781/261	811/271
GCG AAC TAC TTA CTC TAG CTT CCC GGC AAC	AAT TAA TAG ACT GGA TGG AGG CGG ATA AAG
841/281	871/291
TTG CAG GAC CAC TTC TGC GCT CGG CCC TTC	CGG CTG GCT GGT TTA TTG CTG ATA AAT CTG
901/301	931/311
GAG CCG GTG AGC GTG GGT CTC GCG GTA TCA	TTG CAG CAC TGG GGC CAG ATG GTA AGC CCT
961/321	991/331
CCC GTA TCG TAG TTA TCT ACA CGA CGG GGA	GTC AGG CAA CTA TGG ATG AAC GAA ATA GAC
1021/341	1051/351
AGA TCG CTG AGA TAG GTG CCT CAC TGA TTA	AGC ATT GGT AAC TGT CAG ACC AAG TTT ACT
1081/361	1111/371
CAT ATA TAC TTT AGA TTG ATT TAA AAC TTC	ATT TTT AAT TTA AAA GGA TCT AGG TGA AGA
1141/381	1171/391
TCC TTT TTG ATA ATC TCA TGA CCA AAA TCC	CTT AAC GTG AGT TTT CGT TCC ACT GAG GGT
1201/401	1231/411
CAG ACC CCG TAG AAA AGA TCA AAG GAT CTT	CTT GAG ATC CTT TTT TTC TGC GCG TAA TCT
1261/421	1291/431
GCT GCT TGC AAA CAA AAA AAC CAC CGC TAC	CAG CGG TGG TTT GTT TGC CGG ATC AAG AGC
1321/441	1351/451
TAC CAA CTC TTT TTC CGA AGG TAA CTG GCT	TCA GCA GAG CGC AGA TAC CAA ATA CTG TCC
1381/461	1411/471
TTC TAG TGT AGC CGT AGT TAG GCC ACC ACT	TCA AGA ACT CTG TAG CAC CGC CTA CAT ACC
1441/481	1471/491
TCG CTC TGC TAA TCC TGT TAC CAG TGG CTG	CTG CCA GTG GCG ATA AGT CGT GTC TTA CCG
1501/501	1531/511
GGT TGG ACT CAA GAC GAT AGT TAC CGG ATA	AGG CGC AGC GGT CGG GCT GAA CGG GGG GTT
1561/521	1591/531
CGT GCA CAC AGC CCA GCT TGG AGC GAA CGA	CCT ACA CCG AAC TGA GAT ACC TAC AGC GTG
1621/541	1651/551
AGC TAT GAG AAA GCG CCA CGC TTC CCG AAG	GGA GAA AGG CGG ACA GGT ATC CGG TAA GCG

FIGURE 2A (SEQ ID NO: 13)

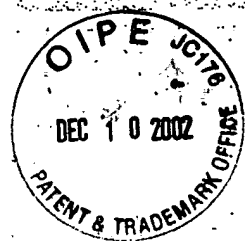


1681/561	1711/571
GCA GGG TCG GAA CAG GAG AGC GCA CGA GGG	AGC TTC CAG GGG GAA ACG CCT GGT ATC TTT
1741/581	1771/591
ATA GTC CTG TCG GGT TTC GCC ACC TCT GAC	TTG AGC GTC GAT TTT TGT GAT GCT CGT CAG
1801/601	1831/611
GGG GGC GGA GCC TAT GGA AAA ACG CCA GCA	ACG CGG CCT TTT TAC GGT TCC TGG CCT TTT
1861/621	1891/631
GCT GGC CTT TTG CTC ACA TGT TCT TTC CTG	CGT TAT CCC CTG ATT CTG TGG ATA ACC GTA
1921/641	1951/651
TTA CCG CCT TTG AGT GAG CTG ATA CCG CTC	GCC GCA GCC GAA CGA CCG AGC GCA GCG AGT
leu pro pro leu ser glu leu ile pro leu	ala ala ala glu arg pro ser ala ala ser
1981/661	2011/671
CAG TGA GCG AGG AAG CGG AAG AGC GCC CAA	TAC GCA AAC CGC CTC TCC CCG CGC GTT GGC
gln OPA ala arg lys arg lys ser ala gln	tyr ala asn arg leu ser pro arg val gly
2041/681	2071/691
CGA TTC ATT AAT GCA GCT GGC ACG ACA GGT	TTC CCG ACT GGA AAG CGG GCA GTG AGC GCA
arg phe ile asn ala ala gly thr thr gly	phe pro thr gly lys arg ala val ser ala
2101/701	2131/711
ACG CAA TTA ATG TGA GTT AGC TCA CTC ATT	AGG CAC CCC AGG CTT TAC ACT TTA TGC TTC
2161/721	2191/731
CGG CTC GTA TGT TGT GTG GAA TTG TGA GCG	GAT AAC AAT TTC ACA CAG GAA ACA GCT atg met
2221/741	2251/751
acc atg att acg cca agc ttg AAG GAT CAT	CTC ATC CAC AAT GTC CAC AAA GAG GAG CAC
thr met ile thr pro ser leu lys asp his	leu ile his asn val his lys glu glu his
2281/761	2311/771
GCT CAT GCC CAC AAC AAG ATC GAT att gtc	gga gga agt gac tcc aga gaa gga gcc tgg
ala his ala his asn lys ile asp ile val	gly gly ser asp ser arg glu gly ala trp
2341/781	2371/791
cct tgg gtc gtt gct ctg tat ttc gac gat	caa cag gtc tgc gga gct tct ctg gtg agc
pro trp val val ala leu tyr phe asp asp	gln gln val cys gly ala ser leu val ser
2401/801	2431/811
agg gat tgg ctg gtg tgg gcc gcc cac tgc	gtg tac ggg aga aat atg gag ccg tct aag
arg asp trp leu val ser ala ala his cys	val tyr gly arg asn met glu pro ser lys
2461/821	2491/831
tgg aaa gca gtg cta ggc ctg cat atg gca	tca aat ctg act tct cct cag ata gaa act
trp lys ala val leu gly leu his met ala	ser asn leu thr ser pro gln ile glu thr
2521/841	2551/851
agg ttg att gac caa att gtc ata aac cca	cac tac aat aaa cgg aga aag aac aat gac
arg leu ile asp gln ile val ile asn pro	his tyr asn lys arg arg lys asn asn asp
2581/861	2611/871
att gcc atg atg cat ctt gaa atg aaa gtg	aac tac aca gat tat ata cag cct att tgt
ile ala met met his leu glu met lys val	asn tyr thr asp tyr ile gln pro ile cys
2641/881	2671/891
tta cca gaa gaa aat caa gtt ttt ccc cca	gga aga att tgt tct att gct ggc tgg ggg
leu pro glu glu asn gln val phe pro pro	gly arg ile cys ser ile ala gly trp gly
2701/901	2731/911
gca ctt ata tat caa ggt tct act gca gac	gta ctg caa gaa gct gac gtt ccc ctt cta
ala leu ile tyr gln gly ser thr ala asp	val leu gln glu ala asp val pro leu leu
2761/921	2791/931
tca aat gag aaa tgt caa caa cag atg cca	gaa tat aac att acg gaa aat atg gtg tgt
ser asn glu lys cys gln gln gln met pro	glu tyr asn ile thr glu asn met val cys
2821/941	2851/951
gca ggc tat gaa gca gga ggg gta gat tct	tgt cag ggg gat tca ggc gga cca ctc atg
ala gly tyr glu ala gly gly val asp ser	cys gln gly asp ser gly gly pro leu met
2881/961	2911/971
tgc caa gaa aac aac aga tgg ctc ctg gct	ggc gtg acg tca ttt gga tat caa tgt gca
cys gln glu asn asn arg trp leu leu ala	gly val thr ser phe gly tyr gln cys ala
2941/981	2971/991
ctg cct aat cgc cca ggg gtg tat gcc cgg	gtc cca agy ttc aca gag tgg ata caa agt
leu pro asn arg pro gly val tyr ala arg	val pro arg phe thr glu trp ile gln ser
3001/1001	3031/1011
ttt cta cat GAG CTC GTA ATT AGC TGA GAA	TTC ACT GGC CGT CGT TTT ACA ACG TCG TGA
phe leu his glu leu val ile ser OPA glu	phe thr gly arg arg phe thr thr ser OPA



3061/1021	3091/1031
CTG GGA AAA CCC TGG CGT TAC CCA ACT TAA	TCG CCT TGC AGC ACA TCC CCC TTT CGC CAG
3121/1041	3151/1051
CTG GCG TAA TAG CGA AGA GGC CCG CAC CGA	TCG CCC TTC CCA ACA GTT GCG CAG CCT GAA
3181/1061	3211/1071
TGG CGA ATG GCG CCT GAT GCG GTA TTT TCT	CCT TAC GCA TCT GTG CGG TAT TTC ACA CCG
3241/1081	3271/1091
CAT ATG GTG CAC TCT CAG TAC AAT CTG CTC	TGA TGC CGC ATA GTT AAG CCA GCC CCG ACA
3301/1101	3331/1111
CCC GCC AAC ACC CGC TGA CGC GCC CTG ACG	GGC TTG TCT GCT CCC GGC ATC CGC TTA CAG
3361/1121	3391/1131
ACA AGC TGT GAC CGT CTC CGG GAG CTG CAT	GTG TCA GAG GTT TTC ACC GTC ATC ACC GAA
3421/1141	
ACG CGC	

FIGURE 2C (SEQ ID NO: 13)



Insert 1

1/1

31/11

CAT CTC ATC CAC AAT GTC CAC AAA GAG GAG CAC GCT CAT GCC CAC AAC (SEQ ID NO: 16)
his leu ile his asn val his lys glu glu his ala his ala his asn (SEQ ID NO: 1)

Insert 2

1/1

31/11

CAT AAC CAT AAC CAT AAC CAT AAC CAT AAC CAT AAC (SEQ ID NO: 17)
his asn his asn his asn his asn his asn his asn his asn (SEQ ID NO: 15)

Insert 3

1/1

31/11

CAT GAT GAT CAT GAT GAT CAT GAT GAT CAT GAT GAT CAT GAT GAT CAT GAT GAT (SEQ ID NO: 18)
his asp asp his asp asp his asp asp his asp asp his asp asp his asp asp (SEQ ID NO: 2)

Insert 4

1/1

31/11

CAT GAG GAG CAT GAG GAG CAT GAG GAG CAT GAG GAG CAT GAG GAG CAT GAG GAG (SEQ ID NO: 19)
his glu glu his glu glu his glu glu his glu glu his glu glu his glu glu (SEQ ID NO: 3)

Insert 5

1/1

31/11

CAT GAT GAG CAT GAT GAG CAT GAG AAC CAT GAG AAC CAT GAG GAT CAT GAG GAT (SEQ ID NO: 20)
his asp glu his asp glu his glu asn his glu asn his glu asp his glu asp (SEQ ID NO: 4)

FIGURE 3